REMARKS

Claims 18, 21-25, 28 and 39-58 were pending in the instant application. Claim 18 has been amended. Claim 28 has been canceled without prejudice herein, therefore obviating objections to this claim. Accordingly, upon entry of the present Amendment, claims 18, 21-25 and 39-58 will be pending in the application, and claims 39-58 remain withdrawn. Applicants respectfully submit that no new matter has been introduced by the foregoing claim amendments.

Amendment and/or cancellation of the claims is not to be construed as acquiescence to any of the objections/rejections set forth in the instant Office Action and was done solely to expedite prosecution of the application. Applicants reserve the right to pursue the claims, as originally filed, or similar claims in this or one or more subsequent patent applications.

Acknowledgement of Withdrawal of Previous Rejections/Objections

Applicants gratefully acknowledge the withdrawal of the following previous rejections:

The Examiner has withdrawn the objection to claim 18 for reciting the term "Figure 1A."

The Examiner has withdrawn the objection to the drawings.

Obviousness-Type Double Patenting

The Examiner has maintained the rejection of claims 18, 21-25, and 28 under the judicially created doctrine of non-statutory obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 7,169,903 (Attorney Docket No: SYNI-008).

The Examiner contends that:

> "[t]hough the scope of the allowed claims is not identical to the instant claims, the allowed claims are directed to a genus of compositions that comprise antibodies of the instant claims, the instant claimed being a species of invention encompassed by the allowed genus, wherein the left half of the two molecules share conserved antigenic domains to which the composition of allowed antibodies would bind in both WTA and LTA of a ribitol wall teichoic acid and a ribitol containing lipoteichoic acids (emphasis added)."

Applicants respectfully traverse.

In response to Applicants' previous argument, the Examiner has observed that WTA and LTA share the antigenic domains shown in the left half of each respective molecule as depicted

in Figure 1 of the instant Office Action (*i.e.* bottom of page 4). The Examiner has taken the position that Applicants previous argument is not persuasive "because monoclonal antibodies specifically bind to the antigen to which they were stimulated, and ribitol teichoic acid and lipoteichoic acid have shared antigens in common to which the monoclonal antibodies would specifically bind." In essence, the Examiner is arguing that the presence of a potential shared antigen (*e.g.* the shared chemical structural motifs of peptidoglycan) is sufficient, in and of itself, to impart overlapping scope between the instant claims and claim 6 of the '903 patent. Applicants do not follow the Examiner's logic. As noted by the Examiner, claim 6 of the '903 patent recites:

> "The composition of claim 1 or 2, further comprising an additional MAb, or an antigen binding fragment thereof, that ***specifically binds to lipoteichoic acid (LTA)*** of Gram-positive bacteria (emphasis added)."

As Applicants pointed out in the previous response, the instant claims are directed, in part, to a pharmaceutical composition comprising a therapeutically effective amount of a monoclonal antibody or an antigen binding fragment thereof that ***specifically binds to ribitol phosphate of wall teichoic acid (WTA) of S. aureus***. It is Applicants' position that the limitation "specifically binds to" in both claims obviates the possibility of a double patenting rejection. The MAbs of the instant invention are not a species of the genus claimed in the '903 patent as alleged by the Examiner; rather, the instant MAbs, as particularly claimed, are directed to subject matter that does not overlap with that of the '903 patent. The Examiner's concern that the presence of a potential shared antigen between LTA and ribitol WTA would allow a MAb of the instant invention to improperly extend the period of exclusivity provided by the '903 patent makes little sense given that both claims require ***specific binding*** to different molecules. In order for the Examiner's concern to be realized, the binding of a hypothetical MAb of the instant invention would have to be substantially directed to the potential shared antigen (*e.g.* the shared chemical structural motifs of peptidoglycan). If this were the case, the MAb would be able to react with ribitol WTA ***and*** to cross-react with LTA. Consequently, it would not meet the limitation "***specifically binds to ribitol phosphate of wall teichoic acid of S. aureus…"*** as particularly recited in the instant pending claims. Nor would it meet the limitation "***specifically binds to lipoteichoic acid (LTA)*** of Gram-positive bacteria" as particularly claimed by the '903 patent, since its binding would not be ***specific*** to either of the claimed molecules. MAb's are directed

against epitopes which represent the 3-Dimensional surface topology of the target protein or molecule. The fact that an anti-WTA MAb binds to an epitope that comprises a moiety found in LTA and in WTA does not mean that the antibody is not specific for WTA. For example, a potential shared moiety may interact with the non-shared regions of the molecule to create a 3-Dimensional surface topology that is unique to the particular molecule (*i.e.* a unique epitope). Nonetheless, in the interest of expediting prosecution of the application, Applicants have added the language "specifically binds to ribitol phosphate ***of*** wall teichoic acid (WTA) of *S. aureus"* to claim 18 to clarify that the antibody binds to the component of WTA that is not found in LTA or Peptidoglycan, therefore, the pending claims are not obvious in view of the cited patent. Thus, Applicants respectfully request favorable reconsideration and withdrawal of the rejection of claims 18, 21-25, and 28.

Amendments/Claim Amendments/New Grounds of Objection/Rejection

Figure 1A

The Examiner has objected to the previous amendment of the legend to Figure 1A on the grounds that the term "such as" constitutes the addition of new matter under 35 U.S.C. § 132(a). Applicants have amended the replacement paragraph so that the last sentences recites "Components of the structure are further labeled with the genes or operons, ~~such as TagO and DltABCD,~~ which are involved in the structure's synthesis including, for example, TagO and DltABCD." Applicants note that a skilled artisan would understand the exemplary meaning of the references to "TagO" and "DltABCD" in Figure 1A. This amendment is believed to address the Examiner's concerns. Applicants request favorable reconsideration and withdrawal of this objection.

Figure 4B

The Examiner has objected to the replacement sheet for Figure 4B submitted with the previous response because it did not include a Mark-up copy. Applicants hereby submit a copy of the replacement sheet with appropriate Mark-up. Applicants apologize for any inconvenience this oversight may have caused the Examiner. Applicants respectfully submit that this objection may now be withdrawn.

Rejection of Claims 18, 21-25, and 28 Under 35 U.S.C. § 103(a) Maintained

The Examiner has maintained the rejection of claims 18, 21-25, and 28 under 35 U.S.C. § 103(a) as being unpatentable over Gotz and Peschel (common inventor, DE19912706) *et al.* in light of English translation, in view of Fischer *et al.* (U.S. Patent No. 6,939,543) in view of Patti *et al.* (U.S. Patent No. 6,703,025). Applicant's respectfully traverse the rejection.

Specifically, the Examiner has stated that:

> "Gotz *et al.* does teach antiserums (see Gotz, DE19912706, col. 6, lines 28-30, and English machine translation) that are specific to recognize alanine-substituted and non-substituted teichoic acids of *S. aureus* to include the wall teichoic acid of S. aureus Sa113 (see Figure 1, Gotz), the wall teichoic acid of S. aureus Sal 13 being a ribitol phosphate wall teichoic acid...
>
> Gotz *et al.* was applied against the claims for teaching the importance of blocking the binding of S. aureus WTA to host animal receptors, <u>for teaching anti-ribitol teichoic acid antibodies induced to the WTA of Staphylococcus aureus strain Sa113</u>, the antibodies recognizing the ribitol teichoic acid antigens to include the D-alanine epitope contained in the ribitol WTA."

Applicants respectfully submit that the Examiner has overstated the teachings of Gotz *et al.*

First, Applicants note that Gotz *et al.* <u>does not teach</u> the importance of blocking the binding of *S. aureus* WTA to host cell receptors, as particularly alleged by the Examiner. Rather, Gotz *et al.* teaches the use of enzymatic inhibitors to block the incorporation of D-Alanine during teichoic acid synthesis (see *e.g.* English machine translation paragraph 8, beginning with the phrase "Since up to the present time the need exists..."). As stated by Gotz *et al.,* the use of such enzymatic inhibitors "leads to the fact that the microorganisms, which are to be fought, develop a sensitivity or higher sensitivity opposite antimicrobial substances." Despite the poor English produced by this machine translation, the Examiner will appreciate from the quoted text that the purpose of Gotz *et al.* is to produce teichoic acid biosynthesis inhibitors for the purposes of compromising the thick peptidoglycan layer typically associated with Gram-positive bacteria so that such bacteria are more susceptible to antimicrobial substances. Accordingly, Gotz *et al.* does not teach antibodies that ***specifically binds to ribitol phosphate of wall teichoic acid (WTA) of S. aureus*** in a ***therapeutically effective amount*** to ***alleviate or block nasal colonization or infection*** by *S. aureus* as presently claimed. Moreover, Applicants respectfully submit that Gotz *et al.* teaches away from the instant invention because that reference is directed to a method of treatment of bacterial

infection with teichoic acid synthesis inhibitors, which is a completely different approach to the problem than that provided by the instant invention. With respect to antibodies, the reference states:

> Another method for searching an effective drug against Gram-positive bacteria in particular uses the reduced biofilm formation on surfaces, especially on plastic or glass surfaces, as a measure of the effect of the potential substance. For this treatment to be controlled microorganisms with a potential drug, and then the formation of biofilms in the form of a provision of slime-forming substances such as the adhesin "polysaccharide intercellular" says general substance of mucus or by determining the number of adhering microorganisms. The detection of the bacteria, the mucus substance or slime-forming substances can be made with dyes, fluorescent groups, radioactive isotopes or with specific antisera.
>
> It is also advantageous to determine the binding ability of teichoic acids on surfaces with the addition of the tested, potential drugs. Proof may by marking the teichoic acids with radioactive isotopes, fluorescent dyes or groups carried or carried out with specific antisera.

One of skill in the art would not read the disclosure of Gotz *et al.* and conclude that the production of antibodies that ***specifically bind to ribitol phosphate of wall teichoic acid (WTA) of S. aureus*** would be an effective means of blocking nasal colonization or infection by *S. aureus*.

Second, Gotz *et al.* does not teach anti-ribitol teichoic acid antibodies induced to the WTA of Staphylococcus aureus strain Sa113 as particularly alleged by the Examiner. As noted in the previous response, the portion of Gotz *et al.* cited by the Examiner states the following:

> "The measurement of the alanine installation can take place direct at the Teichonsauren after treatment of the microorganisms with a potential active ingredient, or it can become the connection of D-alanine to enzymes of the alanine installation and/or the conversion of D-alanine by enzymes of the D-Alanineinbaus certain. ***The proof of the D-alanine or the enzymes can take place with radioactive isotopes, with coloring material or groups of fluorescences, or with antiserums***, which recognize specific alanine-substituted or non-substituted Teichonsauren. Also antiserums used cannot become, which recognize specific enzymes, the alanine bound or bound to have (emphasis added)."

Despite the poor translation, it is clear that Gotz *et al.* do not teach the production of anti-ribitol teichoic acid antibodies induced to the WTA of *Staphylococcus aureus*. Rather, Gotz *et al.* discusses a prophetic means by which the efficacy of the disclosed teichoic acid synthesis inhibitors may be assayed. Given that the methods of Gotz *et al.* are entirely directed to the production of teichoic acid synthesis inhibitors, one of skill in the art would not have used an antibody as a matter of first choice to detect these inhibitors because of the significant amount of time and effort required to produce an antibody, and the fact that the use of such an antibody to assess D-alanine incorporation into teichoic acid is more labor intensive and less sensitive than a radioactively labeled D-alanine precursor. Moreover, there is no indication that an antibody that ***specifically binds to ribitol phosphate of wall teichoic acid (WTA) of S. aureus*** as presently claimed would even be useful to detect D-alanine incorporation into teichoic acid as taught in the reference.

In the instant Office Action, the Examiner has cited column 6, lines 28-30 (same paragraph cited above) and Figure 1 to substantiate the conclusion that Gotz *et al.* discloses anti-ribitol teichoic acid antibodies induced to the WTA of Staphylococcus aureus strain Sa113. Applicants respectfully submit that Gotz *et al.* does not disclose any correlation between the 'antisera' described in the cited paragraph and the ribitol phosphate WTA depicted in Figure 1. As noted in Applicants' previous response, the paragraph that describes the antisera does not provide any disclosure pertaining to ribitol phosphate WTA. Applicants respectfully submit that the Examiner has implied a correlation between the antisera of the cited paragraph and the ribitol phosphate WTA molecule depicted in Figure 1 that is simply not supported by the reference. Accordingly, Gotz *et al.* does not teach an antibody that ***specifically binds to ribitol phosphate of WTA***, let alone in a ***therapeutically effective amount*** to ***alleviate or block nasal colonization or infection*** by *S. aureus* as presently claimed.

As set forth in Applicants' response of October 3, 2008, neither Fischer *et al.* nor Patti *et al.* teach or suggest antibodies which specifically bind the ribitol phosphate of wall teichoic acid of *S. aureus* as set forth in the instant claims, nor do the references teach or suggest the presently claimed pharmaceutical compositions. With respect to antibodies to teichoic acid, Fischer discloses only ***lipoteichoic acids.*** The Examiner's assertion that "Fischer et al teach how to "make and use polyclonal, monoclonal, chimeric, human and humanized antibody for anti-teichoic antibodies" is not accurate; the disclosure of that reference is limited to ***lipoteichoic acids*** only. Specifically, Fischer states at column 5 lines 39-43, "[t]he teichoic

acids related to this invention are lipoteichoic acids which are teichoic acids ***made up of glycerol phosphate*** which is primarily linked to a glycolipid in the underlying cell membrane," not the wall teichoic acids which comprise ***ribitol phosphate*** of the instant invention.

The teachings of Patti *et al.* are concerned with the use of MSCRAMMs or antibodies thereto in multicomponent vaccines. The reference discloses that ligand binding domains in MSCRAMMs are defined by relatively short contiguous stretches of amino acid sequences (motifs) (see Column 2, lines 55-58). In addition to being directed to *protein* components of organisms rather than non-protein components (such as teichoic acids), the reference states that in "[t]o generate an effective immunotherapeutic against *S. aureus,* the vaccine must be multi-component and contain antigens that span the growth cycle as well as include antigens that are expressed by a majority of *S. aureus* isolates." (see Column 6, lines 31-35). Specifically, with respect to teichoic acids, the reference simply states that

> Teichoic acids, lipoteichoic acid for example, which are polymers of glycerol or ribitol phosphate, are linked to the peptidoglycan and can be antigenic. Antiteichoic antibodies are detectable by gel diffusion may be found in patients with active endocarditis due to *S. aureus.*

(see column 22, lines 48-52). In this passage, Patti *et al.* simply note that antiteichoic antibodies may be detected in some patients. This paragraph appears in a section of the application which is introduced by the paragraph stating "a composition is provided that includes the components of any of the above embodiments in combination with a bacterial component, preferably capsular polysaccharides type 5 or type 8, to increase the rate of opsonization and phagocytosis of *S. aureus*." Thus, one of ordinary skill in the art having read the Patti reference would only infer that bacterial components, such as teichoic acids, can be used in conjunction with the ***MSCRAMM peptides*** disclosed therein to increase opsonization of bacteria, not that antibodies to any type of teichoic acid, let alone to WTA, could be used in a composition as presently claimed, i.e., in an amount effective to block nasal colonization with *S. aureus.*

Therefore, Fisher and Patti do not make up for the deficiencies of Gotz. Moreover, a skilled artisan would not have been motivated to combine the cited references. "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art." M.P.E.P. 2143.01, III, citing *KSR International Co. v. Teleflex Inc.*, 550 U.S. 82 USPQ2d 1385, 1396 (2007).

As none of the references teach or suggest an antibody that ***specifically binds to ribitol phosphate of WTA*** or ***the importance of WTA in the pathology of nasal infection and colonization by S. aureus***, a skilled artisan would not have been motivated to make the presently claimed compositions. Moreover, even if one of skill in the art were motivated to combine the references, which applicants deny, there is no teaching or suggestion that an anti-WTA antibody could be present in a composition in an amount sufficient to alleviate or block nasal colonization or infection by *S. aureus* upon administration to a patient. In fact, it was not until applicants generated and characterized the Δ*tagO* WTA deficient mutant (see Examples 1-3 of the Specification) that the criticality of WTA for nasal colonization (see Example 4) by *S. aureus* was understood. By contrast, the disclosure of Gotz *et al.* actually teaches away from the instant inventive concept because it teaches that the preferred method for fight bacterial infection by Gram-positive bacteria is to use teichoic acid synthesis inhibitors to compromise the integrity of the peptidoglycan layer to allow antimicrobial agents better access to the bacteria. The disclosure of Fischer is limited to LTA, and Patti only mentions bacterial components in the context of their use in combination with MSCRAMM peptides. Therefore, one of skill in the art armed with the teachings of these references would not have been motivated to make the claimed compositions comprising antibodies that ***specifically bind to an epitope comprising ribitol phosphate of wall teichoic acid (WTA) of S. aureus***, let alone an amount of such antibodies which are effective to alleviate or block nasal colonization or infection.

In sum, Gotz *et al.,* in combination with Fisher *et al.* and Patti *et al.*, fails to render the instantly claimed invention obvious. Applicants respectfully request that the rejection of claims 18, 21-25, and 28 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

Rejection of Claims 18 and 28 Under 35 U.S.C. § 102(b)

The Examiner has rejected claims 18 and 28 under 35 U.S.C. § 102(b) as being anticipated by Aasjord *et al.* Specifically, the Examiner has stated that "Aasjord *et al.* disclose a composition that comprises a monoclonal antibody specific to Staphylococcus aureus [P-N-acetylglucosaminyl ribitol teichoic acid (see page 246, col. 1, p. 1, bottom of paragraph and col. 1, p.5, "Monospecificity was checked by testing against other staphylococcal antigens ....B-RTA"; and page 247, col. 2, p. l "Monoclonal antibodies to other staphylococcal antigens such as ... B-RTA") , (monoclonal antibody C6 and C7, page 247, Figure 1 and Results) which specifically bind to the glycerol-phosphate backbone of LTA (see page 248, co.. 2, p. 3, last sentence bridging to page 249) together with a pharmaceutical carrier (see page 246 col. 2, p. 1 "0.01M phosphate buffered saline (PBS), pH 7.2)."

Applicants note that Aasjord *et al.* describes "the ***detailed specificities of two such anti-LTA monoclonal antibodies*** and how these reagents can be used to determine against which ***structure of LTA human antibodies are directed*** (introduction, last paragraph; emphasis added)." The Examiner has correctly noted that the Materials and Methods section discusses P-N-acetylglucosaminyl ribitol teichoic acid (p-RTA), but has incorrectly stated that the antibodies of Aasjord *et al.* are directed against p-RTA. Quite the opposite, p-RTA was used by the authors as a negative control to show the ***monospecificity*** of the C6 and C7 ***anti-LTA*** antibodies ***to LTA*** by demonstrating ***that they do not react with p-RTA, PG, or h*** (page 246, column 1, second paragraph from the bottom, "Monospecificity was checked…"). This fact is further emphasized by the first paragraph of the Results section, which state:

> Of the initial 8 hybridoma antibodies reacting with LTA, two were selected for further studies based on their high ELISA titres. They were designated C6 and C7 and isotyped as being IgM K. ***These did not react with the other staphylococcal antigens tested*** [*i.e.* PG, p-RTA, and h] (emphasis added)."

Accordingly, the reference does not teach compositions comprising antibodies that ***specifically bind to ribitol phosphate of wall teichoic acid (WTA) of S. aureus*** in a ***therapeutically effective amount*** to ***alleviate or block nasal colonization or infection*** by *S. aureus* as presently claimed. Applicants respectfully request that the rejection be withdrawn.

SUMMARY

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicants' Attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

In addition, Applicants include herewith authorization to charge fees associated with new claims and the extension of time with which to respond, to Deposit Account No. 12-0080, under Order No. SYNI-007RCE3. The Director is also hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to Deposit Account No. 12-0080, under Order No. SYNI-007RCE3.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Dated: May 17, 2010

Respectfully submitted,

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Attachments:
Replacement Sheet for Figure 4B